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PATENT COOPERATION TREATY

REC'D 29 JUN 2000
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P 414 PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/00522	25/03/1999	25/03/1998
International Patent Classification (IPC) or national classification and IPC.		
G01N35/00		
Applicant		
STERGAARD, Steen et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 25 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/10/1999	27.06.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Loades, M Telephone No. +49 89 2399 2184

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/00522

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-58	as originally filed			

Claims, No.:

1-80	as received on	13/06/2000	with letter of	13/06/2000

Drawings, sheets:

5/18,6/18, 14/18-18/18	as originally filed			
1/18-4/18, 7/18-13/18	as received on	30/04/2000	with letter of	30/04/2000

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to b non-obvious), or to be industrially applicable have not been xamined in respect of:

☐ the entire international application.

☒ claims Nos. 12,13,50,51,62-64,80.

because:

☒ the said international application, or the said claims Nos. 62-64,80 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 12,13,50,51 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1--11, 14-49, 52-61, 65-79
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5, 6, 15-17, 24-49, 52-61, 65-79
	No:	Claims	1-4, 7-11, 14, 18-23
Industrial applicability (IA)	Yes:	Claims	1-11, 14-49, 52-61, 65-79
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the d scription, are made:

see s parate she t

Re It m I
Basis of the opinion

Support for claims 27, 31 could not be found.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12, 13, 50, 51: not clear - see Item VIII
Claims 62-64,80: Rule 67(iv), and not clear.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The following documents are referred to in this report:
   - D1: WO 98 10267 A (BLANKENSTEIN GERT ;TECHNICAL UNIVERSITY OF DENMAR (DK)) 12 March 1998
   - D2: WO 93 24231 A (BIOSITE DIAGNOSTICS INC) 9 December 1993 & US 5 885 527 A (BUECHLER K. F.) 23 March 1999
   - D3: WO 93 22053 A (UNIV PENNSYLVANIA) 11 November 1993
   - D4: WO 98 46438 A (BOUSSE LUC ;CHOW CALVIN Y H (US); KNAPP MICHAEL R (US); PARCE J WA) 22 October 1998 & US 5 885 470 A (BOUSSE LUC ET AL) 23 March 1999

2. Review of the prior art documents:

D1 describes a microflow system with means for separating particles by application of an e.g. magnetic field. Virtually all examples involve a flowing fluid system, in which liquid carrying particles flows through a flow tube. In the embodiment of fig. 11 (see also description on page 25-26 and page 10, lines 11-17), although referred to as a microflow system, the tube is filled up from one end, and a field applied from the other end to draw particles therealong and distribute them to permit observation.
D2, D3 and D4 all describe micro systems in which there is through flow of (particle carrying) liquid.

3. Novelty and inventive step

Claim 1: None of the documents anticipates claim 1.

In D1, the fig. 11 embodiment, and as described on page 10, paragraph 4, where it is stated that the tube is closed at the end having the magnet, it would appear that, once the system has been filled up with fluid, there could be no transfer of fluid from a first to a second compartment, otherwise the particles could not be distributed along the tube. When the particles are moved, although they are caused to distribute along the tube, they do not seem to be moved into the second compartment (if this is what feature ii of claim 1 means). Thus claim 1 seems to be novel in the light of D1.

However, it would appear obvious that with a strong enough field, the particles would move into the second compartment.

Dependent claims:

The dependent claims 2-4,6-11,14, 18-23 seem to relate to mere design modifications, consequential features of the basic system of claim 1, or conventional features, and thus do not add anything inventive to this claim:

claims 2,3: feature known from D1 (see e.g. page 9, line 26);

claim 4: feature seems to be known from D1

claim 7: feature known from D1.

claims 8,9: conventional in the art (see e.g. D1)

claims 10, 11: implied on page 10, para 4, of D1.

claim 14: obvious from a consideration of D1.

claims 18,19: seem to be obvious, considering materials used for this type of apparatus.

claims 20-24: conventional.

Claim 5 (if interpreted in a manner which restricts the claim to a concrete construction), and claims 6,15-17: these relate to arrangements which do not appear to be hinted at by D1.

Claim 24:

Although various features of claim 24 are known in the same manner as with claim 1 as indicated above, the arrangement of D1, fig.11 and page 10, para. 4, does not hint at a method in which a further liquid carrier is input into the second compartment, and

so claim 24 can be.considered new and involving an inventive step.

Claims 25-49, 52-61, 65-79, being dependent on claim 24, can also be considered new and inventive.

Re Item VIII

Certain observations on the international application

Lack of clarity; inconsistency between claims and description:

a. One of the more important features of claim 1 appears to be the idea of moving the particles from one compartment to another, without transfer of liquid carrier during the particle movement. However, this feature is confused by conflicting references in the description: e.g. page 57, lines 18-19, refers to the liquid not moving faster than the particles, as does page 14, lines 1-2.
b. Claim 1 is not clear since it defines the invention in terms of a result to be achieved, without defining the concrete technical features (of the construction of the apparatus) which achieve this result.
c. In view of the reference to solid walls in claim 1, the description at page 9, line 11 should have been revised.
d. Claim 24 contains similar obscurities to those mentioned in a. and b. above.
e. Claims 2 , 3 and 5 are not clear, since they refer to features which are present only in use of the apparatus, i.e. not permanent features of the construction of the system.
f. It is not clear how the arrangements of claims 12,13, (and 50,51) would function within the scope of claim 1.
g. Pages 11-29 contain various statements defining an invention, which do not correspond with the claims. This leads to ambiguity with regard to the scope of the invention. These pages should have been comprehensively revised to correspond with the amended claims.

PATENT CLAIMS

1. Micro system comprising a system of operably linked, interconnected compartments wherein at least one reagent immobilised on at least one particle is capable of contacting an analyte comprised in a liquid carrier, the micro system comprising

i) a first compartment and a second compartment, wherein each of the first and second compartments are defined by solid walls and at least one opening for passing liquids between the compartment and the exterior,

ii) means for subjecting at least part of the system to a field so as to move at least one particle between the first and the second compartment, and

iii) a passage defined between the first compartment and the second compartment so as to allow at least one particle to be moved through the passage from I) a first liquid carrier comprised in the first compartment to ii) a second liquid carrier comprised in the second compartment, substantially without any transfer of liquid carrier between the first and the second compartment during particle movement.

2. System according to claim 1 further comprising at least one particle with surface properties suitable for immobilising at least one reagent thereon.

3. System according to any of the preceding claims and further comprising at least one reagent suitable for being immobilised on the surface of the at least one particle,

4. System according to any of the preceding claims, wherein the first compartment is a storage compartment for storage of at least one particle.

5. System according to any of the preceding claims, wherein the second compartment comprises a liquid sample comprising an analyte capable of interacting with a reagent immobilised on at least one particle.

6. System according to any of the preceding claims, wherein the second compartment further comprises a second opening for passing liquids between the compartment and the exterior.

7. System according to any of the preceding claims, wherein the system comprises at least one field generating means adapted to apply a field to at least a part of the system, and at least one particle being at least partly made from a material susceptible to the generated field.

8. System according to claim 7, wherein the generated field is a magnetic field.

9. System according to claim 7, wherein the field generating means comprise at least one electromagnet.

10. System according to claim 7, wherein the field generating means comprises two electrodes in electrical contact with the liquid in the system so that the field generating means are activated by applying an electrical potential difference between the two electrodes and at least one particle is moved by electrophoresis.

11. System according to claim 7, wherein the field generating means comprises two electrodes which are not in electrical contact with the liquid in the system so that the field generating means are activated by applying an electrical potential difference between the two electrodes and at least one particle is moved by dielectrophoresis.

12. System according to claim 7, wherein th field is generated by centrifugation of the system.

13. System according to claim 7, wherein the field is a gravitational field.

14. System according to any of claims 1 to 13 and further comprising detection means for detecting properties of at least one reagent immobilised on the surface of at least one particle.

15. System according to any of claims 1 to 14 and further comprising a third compartment for performing the detection of the properties of at least one reagent immobilised on the surface of at least one particle with the detection means, the third compartment comprising

i) an opening for passing liquids between the compartment and the exterior,

ii) an area that is transparent to allow of optical access from the exterior to the interior of the compartment, and

iii) a passage defined between the second compartment and the third compartment so as to allow particles to be moved between the second compartment and the third compartment,

iv) the means for subjecting at least a part of the system to a field being adapted for moving at least one particle between the second compartment and the third compartment by the field.

16. System according to any of claims 1 to 15 and comprising

i) at least one auxiliary compartment, the auxiliary compartment comprises an opening for passing liquids between the compartment and the exterior, and

ii) a passage defined b tween the auxiliary compartment and one of the other compartments so as to allow particles to be moved between the compartment and the auxiliary compartment,

iii) the means for subjecting at least part of the system to a field being adapted for moving at least one particle between the auxiliary compartment and the compartment by the field.

17. System according to any of claims 7 to 16, wherein the field generating means of the system are adapted for moving at least one particle back and forth between compartments between which a passage is defined.

18. System according to any of claims 1 to 17, wherein one of the compartments is adapted for letting electromagnetic radiation of certain wavelengths reach the liquid contained in the compartment.

19. System according to claim 18, where the electromagnetic radiation is light.

20. System according to any of claims 1 to 19, wherein at least one particle is of a mean diameter of 1-200 micro meter.

21. System according to any of claims 1 to 20, wherein the cross-sectional dimensions of the compartments are within from 100 to 1000 micro meter.

22. System according to any of claims 1 to 21, wherein the system is manufactured from materials that are non-magnetic.

23. System according to any of claims 1 to 22, wherein the system is manufactured from materials that are non-autofluorescent.

24. A method of moving a particle comprising at least one reagent immobilised thereon between a first compartment and a second compartment of a micro system comprising a plurality of operably linked compartments, the method comprising the steps of

i) providing at least one particle with at least one reagent immobilised thereon,

ii) introducing the particle into a first compartment,

iii) introducing a first liquid carrier into the first compartment,

iv) introducing a second liquid carrier into a second compartment,

v) subjecting the micro system to a field exerting a force on at least one particle susceptible to the field,

vi) moving by means of the force at least one particle from the first liquid carrier comprised in the first compartment into the second liquid carrier comprised in the second compartment, substantially without any transfer of liquid carrier between the first and the second compartment during particle movement.

25. Method according to claim 24, wherein the second liquid carrier comprises a liquid sample comprising an analyte.

26. Method according to claim 25 and further comprising the step of contacting the analyte comprised in the second liquid carrier with at least one reagent immobilised on at least one particle.

27. Method according to claim 26 and comprising th further step of moving from the second liquid carrier comprised in the second compartment and into the first liquid carrier comprised in the first compartment at least one particle with at least one reagent immobilised thereon and contacting the analyte.

28. Method according to claim 27 and comprising the even further step of washing the analyte in the first compartment comprising the first liquid carrier.

29. Method according to claim 27 and comprising the further step of purifying the analyte in the first compartment comprising the first liquid carrier.

30. Method according to claim 27 and comprising the further step of detecting the analyte in the first compartment comprising the first liquid carrier.

31. Method according to any of claims 28 to 30, wherein the first liquid carrier during the even further step comprises an amount of the second liquid carrier that does not interfere with the efficacy of the even further step.

32. Method according to claim 24, wherein the first liquid carrier comprises a liquid sample comprising an analyte.

33. Method according to claim 32 and further comprising the step of contacting the analyte comprised in the first liquid carrier with at least one reagent immobilised on at least one particle.

34. Method according to any of claims 32 and 33, wherein the second liquid carrier is introduced into the second compartment prior to or simultaneously with the analyte in the first liquid carrier being contacted with the reagent on at least one particle.

35. Method according to any of th preceding claims, wherein th particle and the first liquid carrier are entered into the first compartment at least essentially simultaneously.

36. Method according to any of the preceding claims, wherein the particle and the first liquid carrier are entered into the first compartment sequentially in any order.

37. Method according to any of the preceding claims, wherein the particle is disposable.

38. Method according to any of the preceding claims, wherein the particle is reconstitutable from a long term storage stable condition prior to being introduced into the first compartment.

39. Method according to claim 38, wherein the storage stable condition is a frozen condition.

40. Method according to claim 39, wherein the condition is freeze dried.

41. Method according to claim 39, wherein the condition is cryoprotected.

42. Method according to any of the preceding claims, wherein the first liquid carrier or the second liquid carrier is selected from the group consisting of water, saline, any physiologically acceptable aqueous solvent, any pharmaceutically acceptable aqueous solvent, any organic solvent, including any mixture thereof.

43. Method according to any of the preceding claims, wherein the first liquid carrier and the second liquid carrier is selected from the group consisting of water, saline, any physiologically acceptable aqueous solvent, any

pharmaceutically acceptable aqueous solvent, any organic solvent, including any mixture th_reof.

44. Method according to any of the preceding claims, wherein the reagent is selected from the group consisting of a nucleic acid such as a DNA, RNA or PNA molecule, including any derivative or part thereof, a polypeptide, including any derivative or part thereof including peptides and epitopes, a receptor moiety such as a receptor capable of binding a cell differentiation factor such as a cytokine or a lymphokine, an antibody including a chimeric antibody, a heterodimeric antibody, and a monoclonal antibody, including any binding fragments thereof.

45. Method according to any of the previous claims, wherein the step of subjecting the system to a field comprises the step of positioning at the system field generating means for generation of a field that is subjected to at least a part of the system.

46. Method according to claim 45, wherein the step of subjecting the system to a field comprises the step of generating a magnetic field.

47. Method according to claim 45, wherein the step of positioning field generating means at the system comprises positioning an electromagnet at the system, and wherein the step of subjecting the system to a field comprises activating the electromagnet with an electric current.

48. Method according to claim 45, wherein the step of positioning field generating means at the system comprises positioning two electrodes in electrical contact with the liquid carriers in the system, and wherein the step of subjecting the system to a field comprises the step of supplying an electric potential between the two electrodes so that at least one particle is moved by electrophoresis.

49. Method according to claim 45, wherein the step of positioning field generating means at the system comprises positioning two electrodes at the system in such a way that they are not in electrical contact with the liquid in the system, and wherein the step of subjecting the system to a field comprises the step of supplying an electric potential between the two electrodes so that at least one particle is moved by dielectrophoresis.

50. Method according to claim 45, wherein the step of subjecting the system to a field comprises the step of centrifugation of the system.

51. Method according to claim 45, wherein the step of subjecting the system to a field comprises the step of subjecting the system to the field of gravitation.

52. Method according to any of claims 45 to 51 and comprising the further step of monitoring properties of at least one particle during sample interaction.

53. Method according to any of claims 45 to 52 and comprising the further step of monitoring properties of at least one particle after sample interaction.

54. Method according to any of the preceding claims, wherein the system further comprises a third compartment that is interconnected with the second compartment.

55. Method according to claim 54 and comprising the further steps of moving at least one particle by means of the field into the third compartment, and monitoring the properties of at least one particle situated in the third compartment.

56. Method according to any of the previous claims, wherein the system further comprises a secondary interaction-compartment that is

Replacement sheet (Rule 66.8)

interconnected with the second compartment, and wherein the method comprises, prior to the step of monitoring the properties of at least one particle, the further steps of

i) moving at least one particle by means of the field into the secondary interaction-compartment of the system, and

ii) allowing at least one particle to interact with a liquid contained in the secondary interaction-compartment so as to make the result of the interaction between the reagents and the content of the liquid sample detectable by detection means.

57. Method according to any of the preceding claims, wherein the system further comprises a washing-compartment that is interconnected with any of the other compartments, and wherein the method comprises the further steps of

i) moving at least one particle into the washing-compartment of the system by means of the field, and

ii) allowing at least one particle to interact with a liquid contained in the washing-compartment so as to remove unwanted material from at least one particle.

58. Method according to any of the preceding claims, wherein one of the compartments is adapted for letting electromagnetic radiation of certain wavelengths reach the liquid contained in the compartment, and wherein the method further comprises the step of subjecting at least one particle to electromagnetic radiation of a wavelength suitable for causing photoactivation.

59. Method according to any of th preceding claims, wherein at least one particle is of a mean diameter of from 1 to 200 micro meter.

60. Method according to any of the preceding claims, wherein the cross-sectional dimensions of the compartments are within from 100 to 1000 micro meter.

61. Method according to any of claims 25 to 60, wherein the analyte is a biological organism, or a part thereof, selected from the group consisting of a cell, an infectious agent including a virus, and a parasite, including any part or combination thereof.

62. Method according to claim 61, wherein the organism is a mammalian organism.

63. Method according to claim 62, wherein the mammalian organism is a human or an animal.

64. Method according to claim 62, wherein the mammalian organism is a human or animal cell, including any derivative thereof.

65. Method according to claim 62, wherein the mammalian organism is a virus or a parasite capable of being harboured in or replicated in a human or animal cell, or a derivative thereof.

66. Method according to claim 65, wherein the parasite is a parasitic fungi,.

67. Method according to any of claims 53, wherein the cell, virus or parasite is pathogenic or potentially lethal.

68. Method according to claim 61, wherein the organism is a microbial organism.

69. Method according to claim 68, wh_rein the microbial organism is a eukaryotic microbial organism.

70. Method according to claim 68, wherein the microbial organism is a prokaryotic microbial organism.

71. Method according to claim 68, wherein the microbial organism is a potentially lethal microbial organism.

72. Method according to claim 68, wherein the microbial organism is a pathogenic organism.

73. Method according to any of claims 25 to 60, wherein the analyte is an antigen.

74. Method according to any of claims 25 to 60, wherein the analyte is an antibody indicative of a predetermined cell type.

75. Method according to any of the preceding claims and comprising the further step of performing, in at least one of the compartments, a method of amplifying a biological compound by a plurality of thermo cyclic reactions at predetermined temperatures.

76. Method according to claim 75, wherein the thermo cyclic reactions are suitable for i) annealing nucleic acids, ii) extension reactions suitable for synthesising a nucleic acid, and iii) denaturing reactions suitable for separating synthesised double stranded nucleic acids.

77. Method according to any of the preceding claims, wherein the micro system is th syst m according to any of claims 1 to 23.

78. Method according to any of the previous claims and comprising the further step of analysing the content of a liquid contained in a container, the method comprising the further steps of

(a) mixing particles with the liquid so as to obtain a substantially even distribution of the particles in at least a part of the liquid, the particles being at least partly made from a material susceptible to a field, such as a magnetic field or an electric field, and having at least one reagent immobilised on a plurality of the particles,

(b) allowing the reagent immobilised on the particles to interact with the content of the liquid,

(c) applying a field to which the particles are susceptible to at least a part of the container so as to move at least one of the particles through an opening of the container to extract at least one particle from the container,

(d) moving at least one particle through a liquid filled passage to detection means for detecting properties of the reagents on the at least one particle, and

(e) detecting properties of the reagent on the at least one extracted particle in order to determine whether these properties have changed due to the interaction, so as to perform an analysis of the liquid.

79. Method according to claim 78, wherein the steps (c) to (e) are repeated at least once after elapse of a predetermined time period so as to provide a monitoring of a possible ongoing process involving the liquid.

80. Method of diagnosing a condition in an individual by d tecting an analyte in a sampl , the diagnostic method comprising

a) providing a sample from the individual, and

b) a method for detecting an analyte in the sample, the presence of the analyte being an indication of the individual having contracted the condition, the method of detection comprising the steps of

i) moving according to the method of any of claims 24 to 77 a particle comprising at least one reagent immobilised thereon into a liquid sample that is contained in a micro system comprising a system comprising a plurality of operatively linked compartments, and

ii) contacting the reagent with the analyte comprised in a sample in the form of a first liquid carrier or a second liquid carrier for the purpose of

iii) detecting diagnostically the analyte contacted by the reagent, and

iv) diagnosing the condition.

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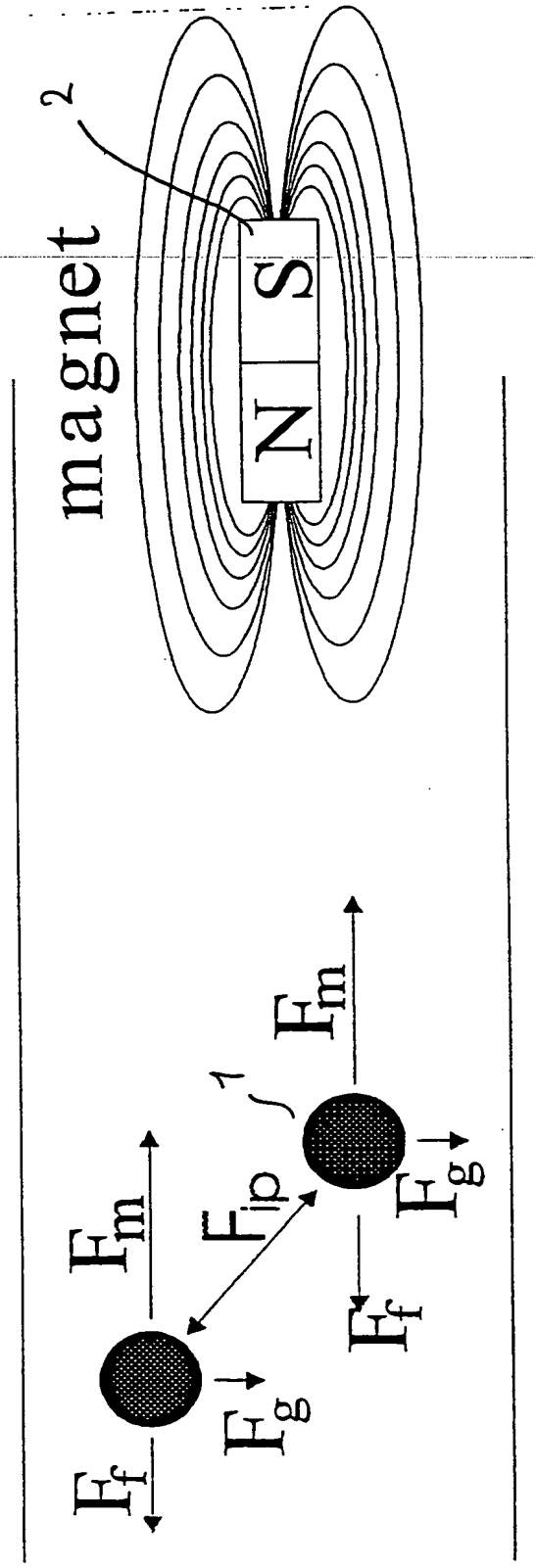

Fig. 1

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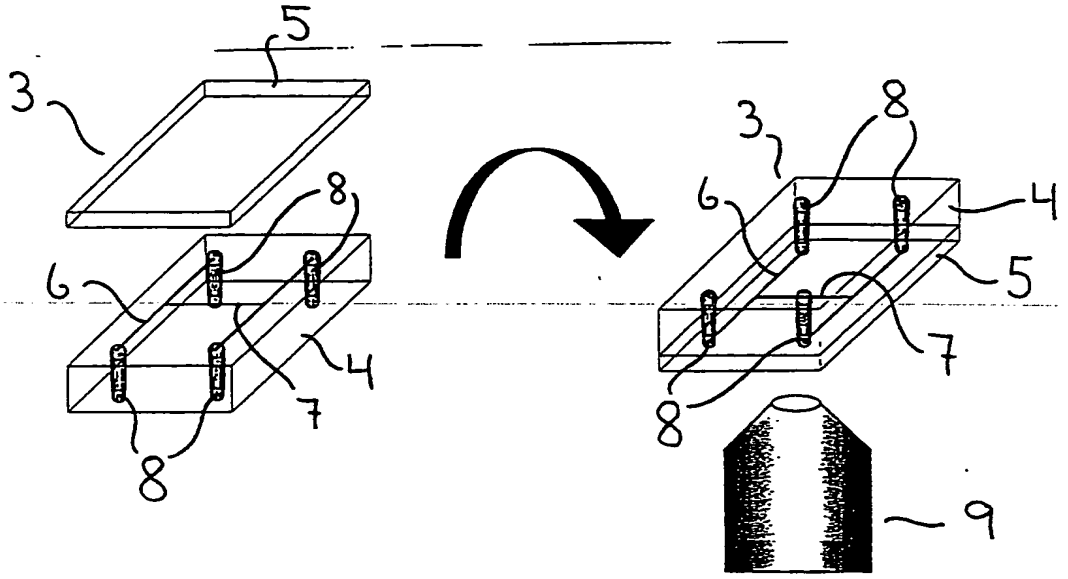

Fig. 2

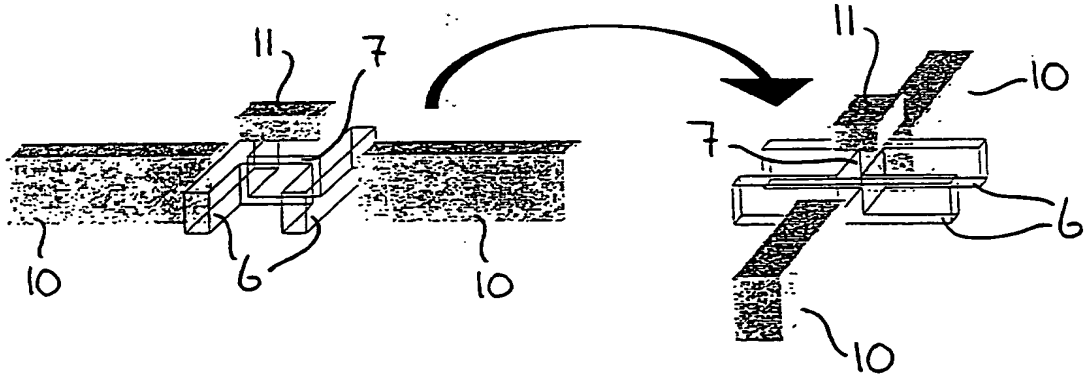

Fig. 3

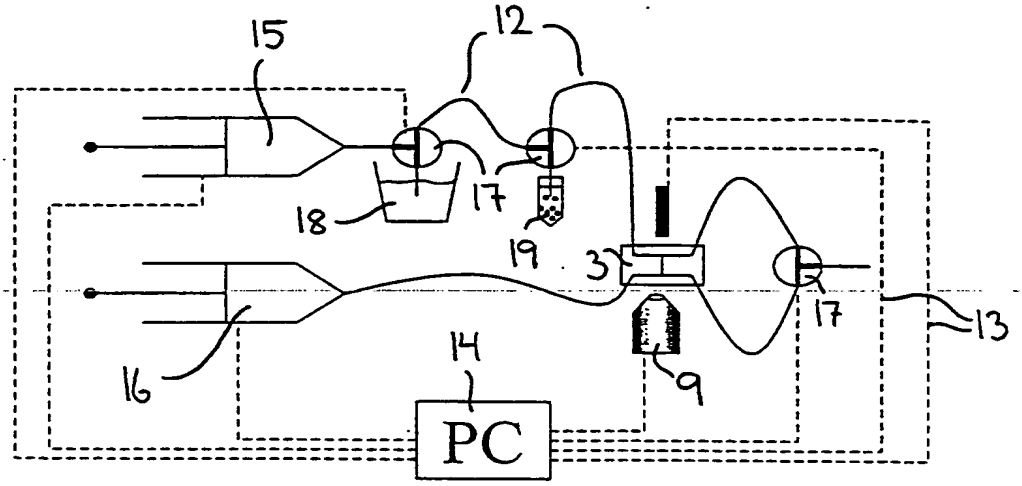

Fig. 4

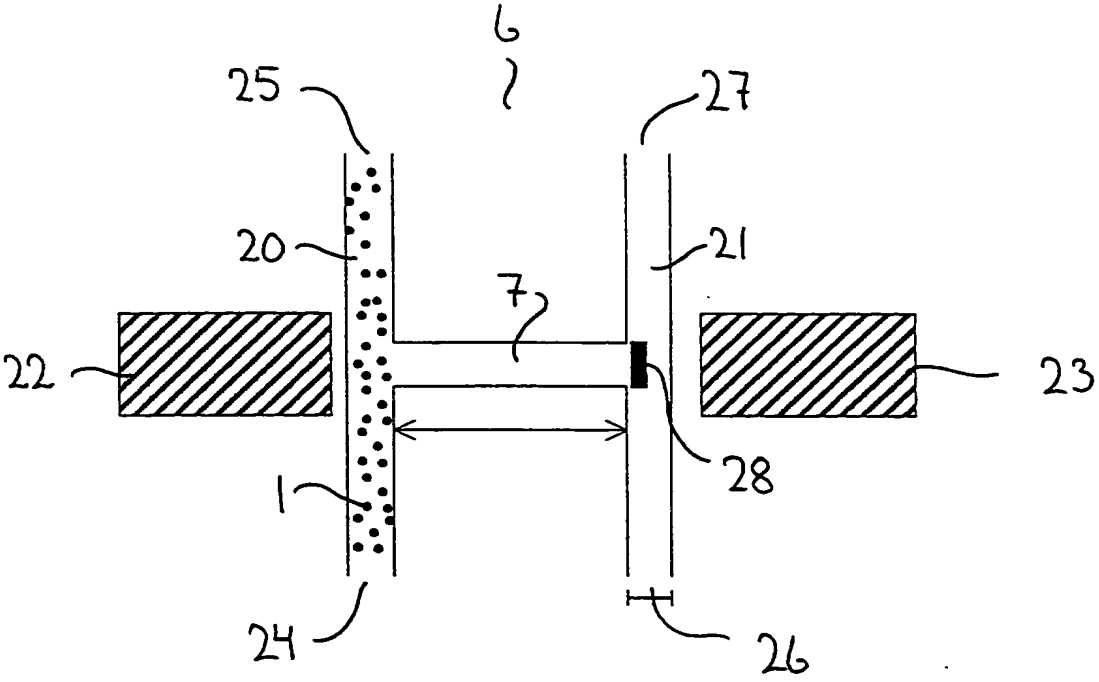

Fig. 5

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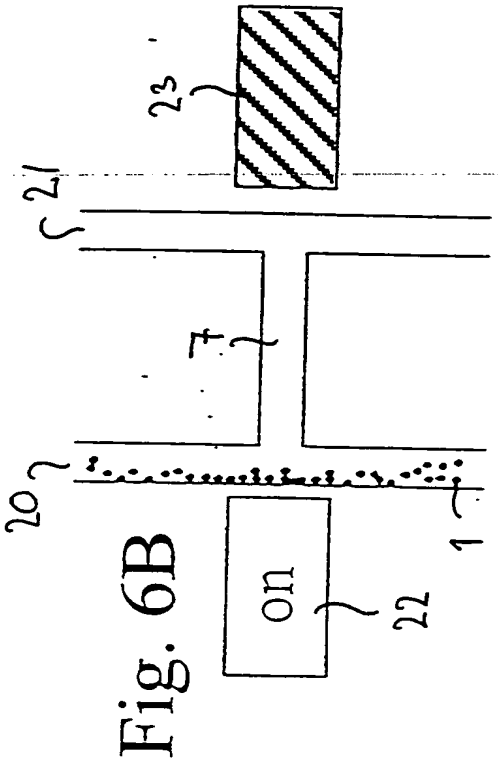


Fig. 6B

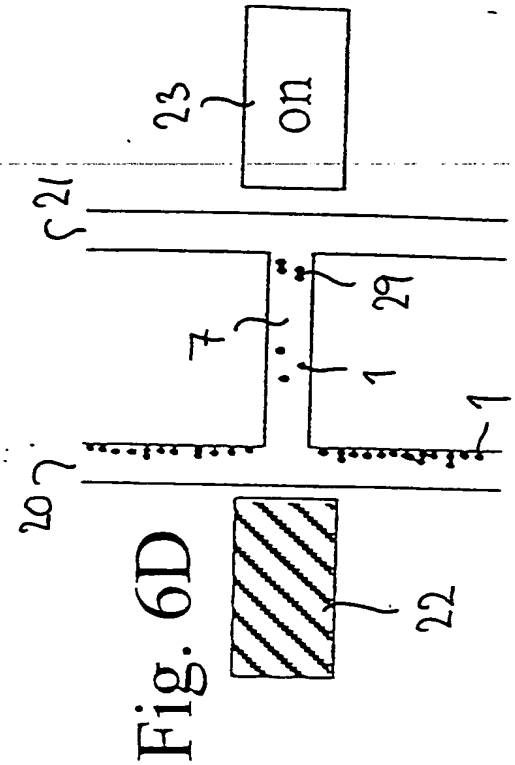


Fig. 6D

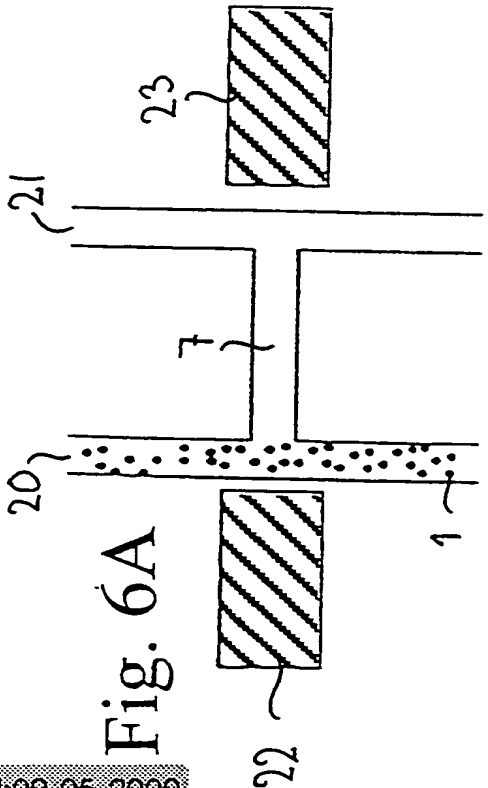


Fig. 6A

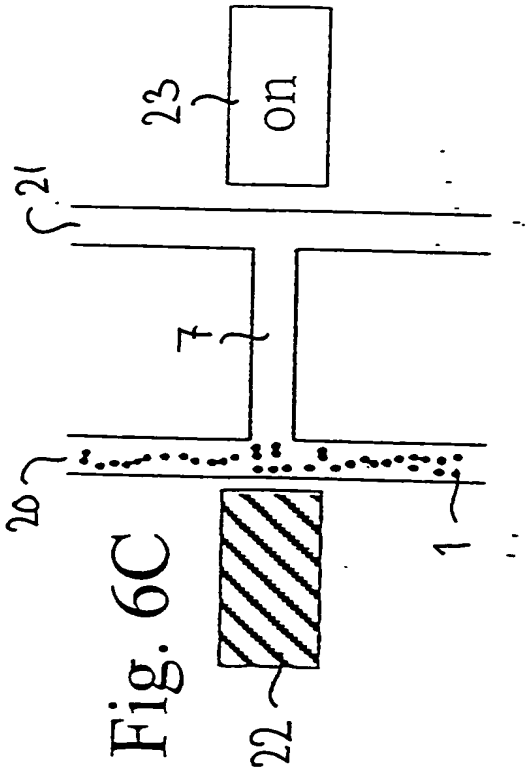
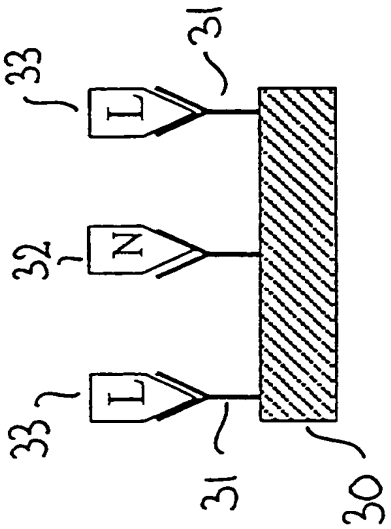


Fig. 6C

Replacement sheet (Rule 66.8)

Fig. 10a



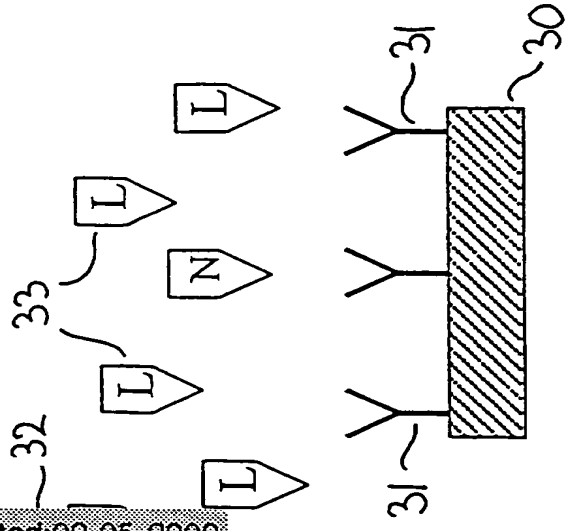
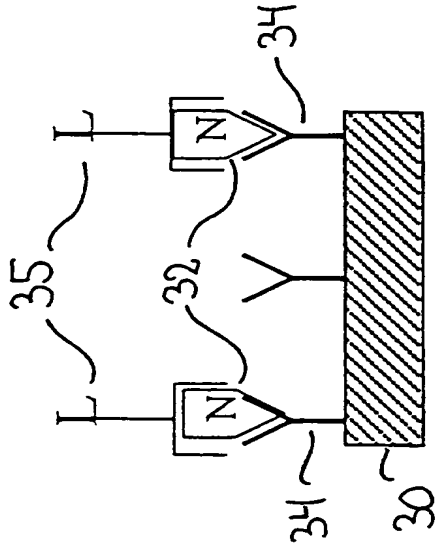
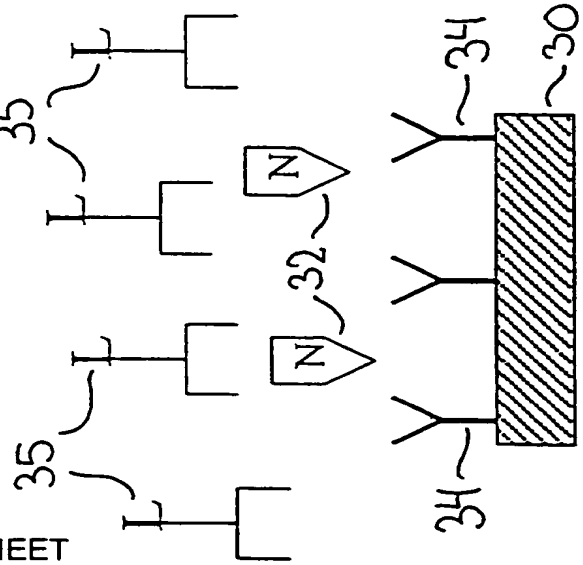


Fig. 10b





Replacement sheet (Rule 66.8)

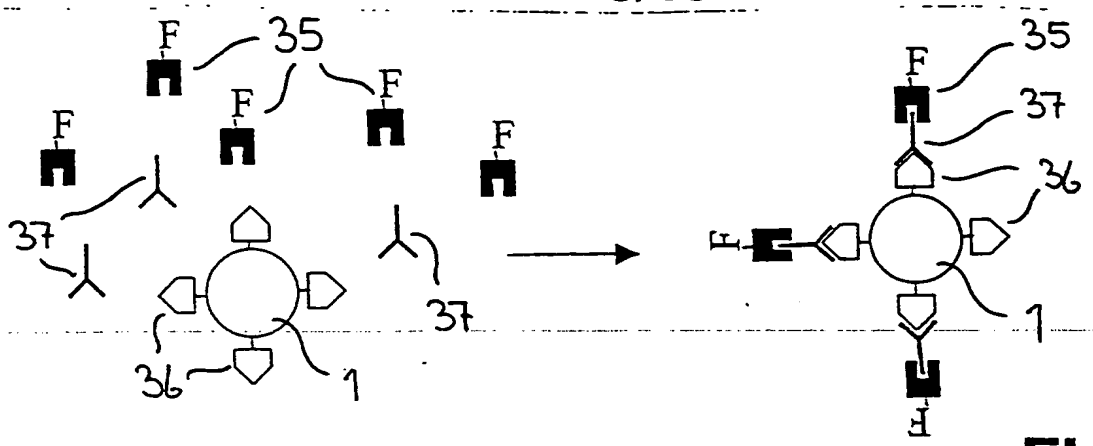


Fig. 11

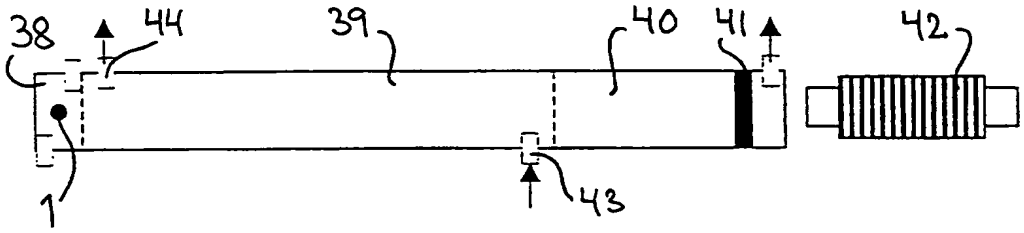


Fig. 12a

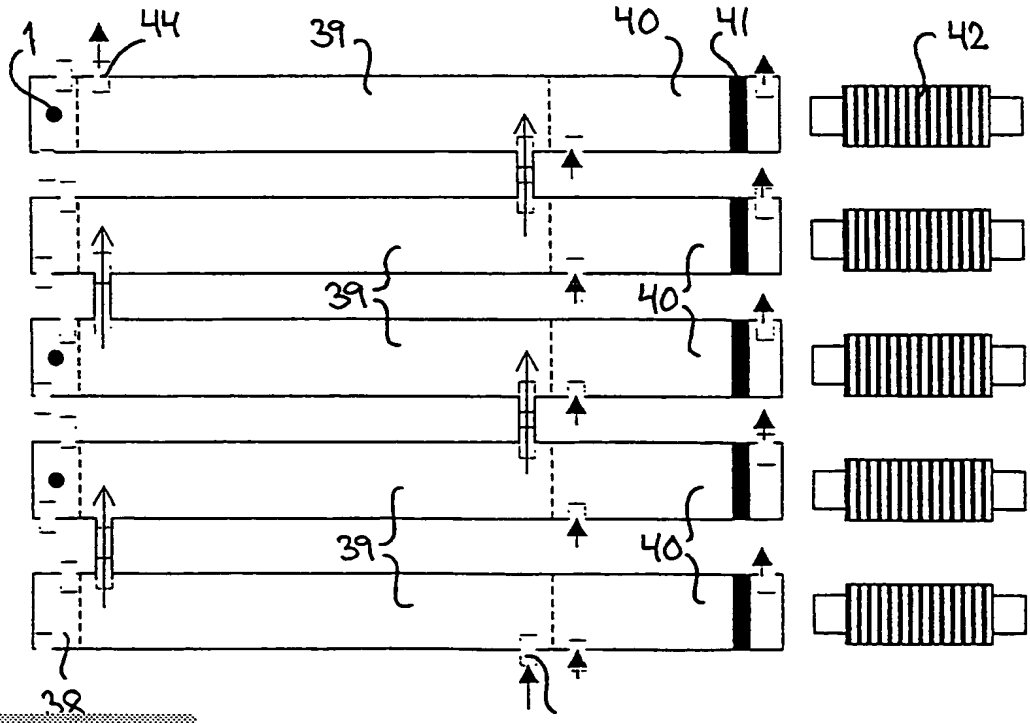


Fig. 12b

Replacement sheet (Rule 66.8)

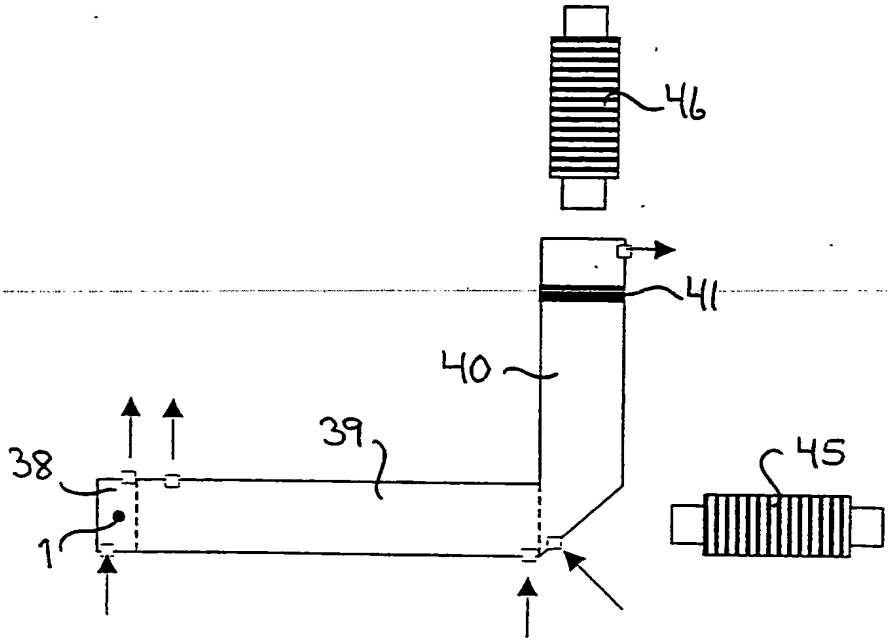


Fig. 13

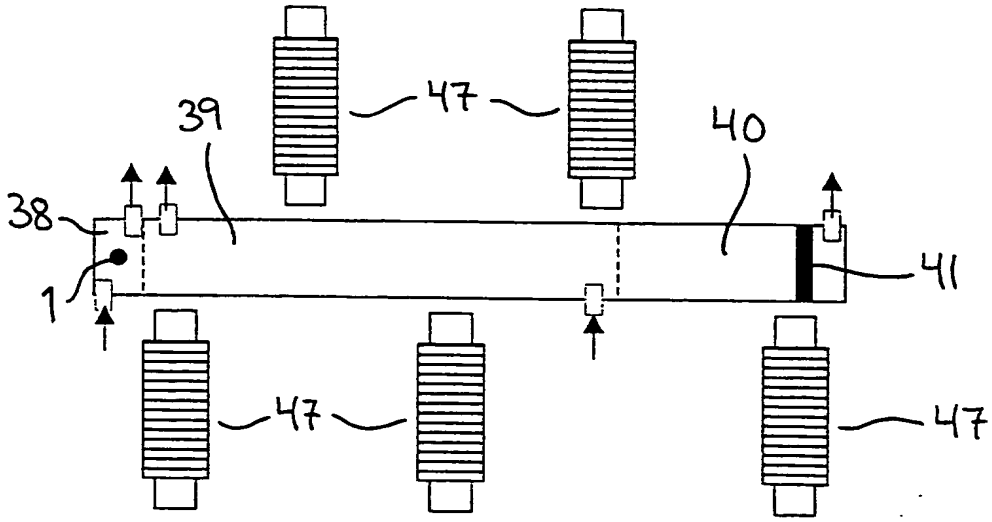


Fig. 14

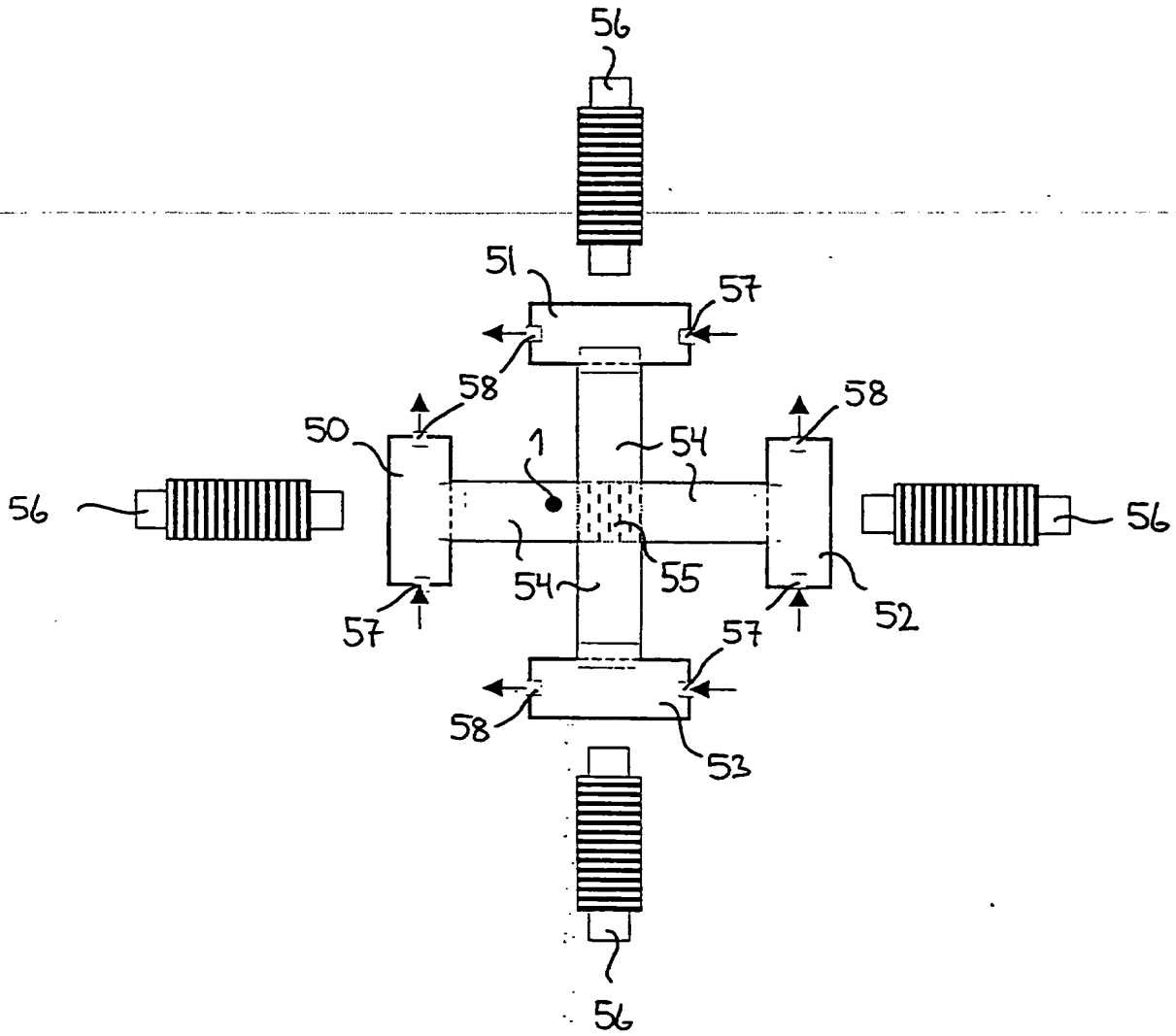


Fig. 15

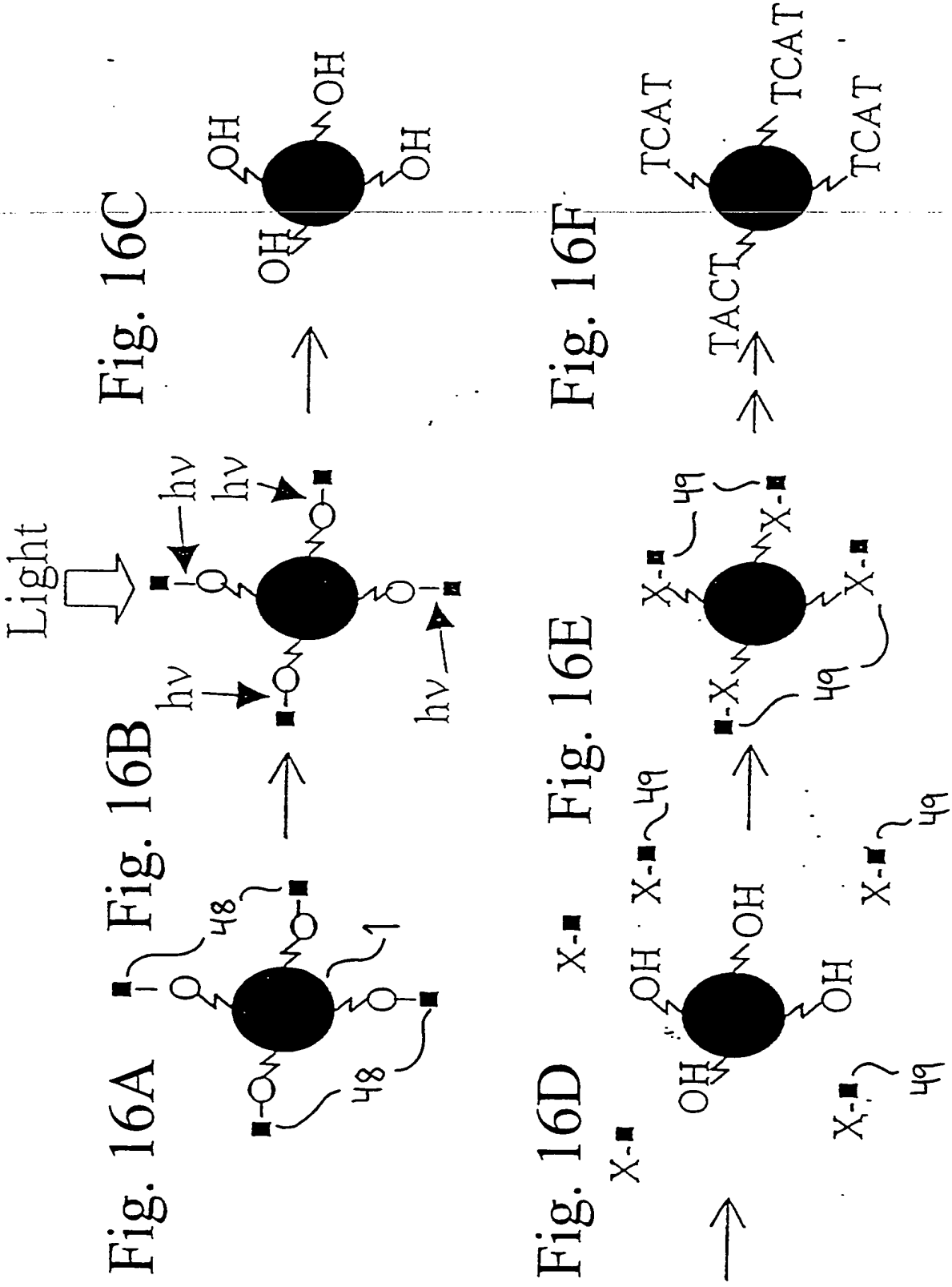


Fig. 16A
48
48
1
Fig. 16B
Light
hν
hν
hν
hν
Fig. 16C
OH
OH
OH
OH
Fig. 16D
X-
X-
49
49
49
X-
X-
OH
OH
OH
Fig. 16E
X-
X-
X-
X-
49
49
Fig. 16F
TCAT
TCAT
TCAT
TACT

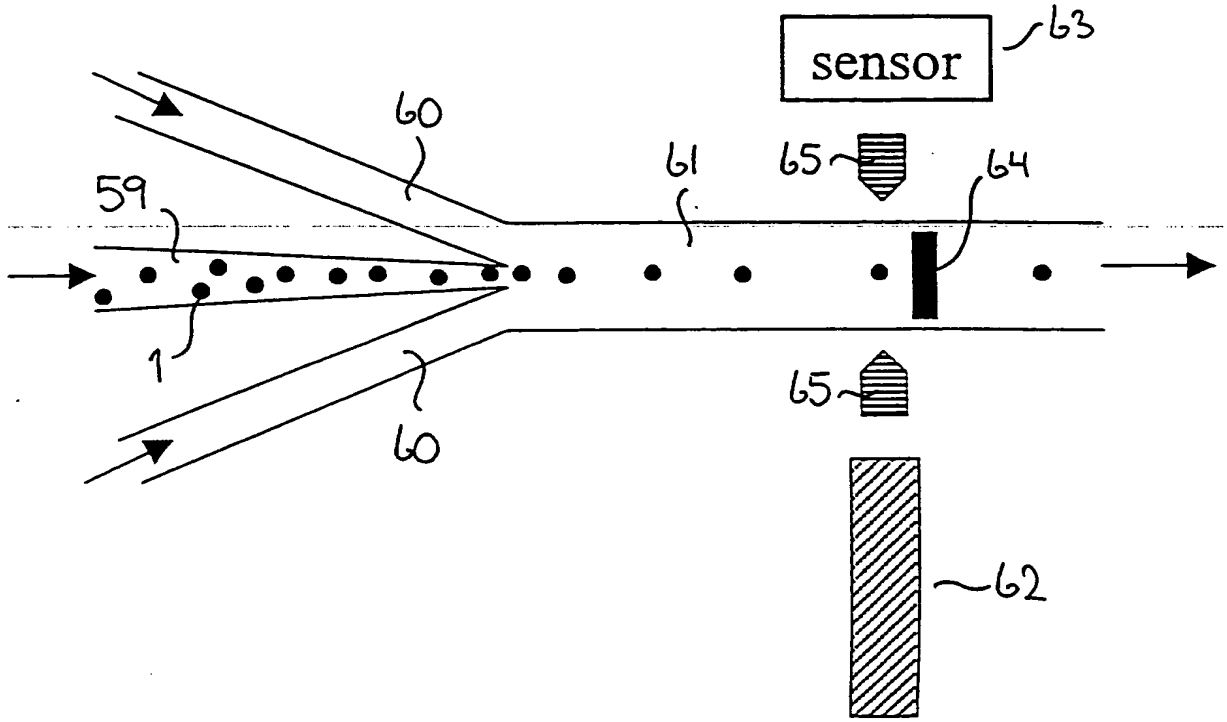


Fig. 17

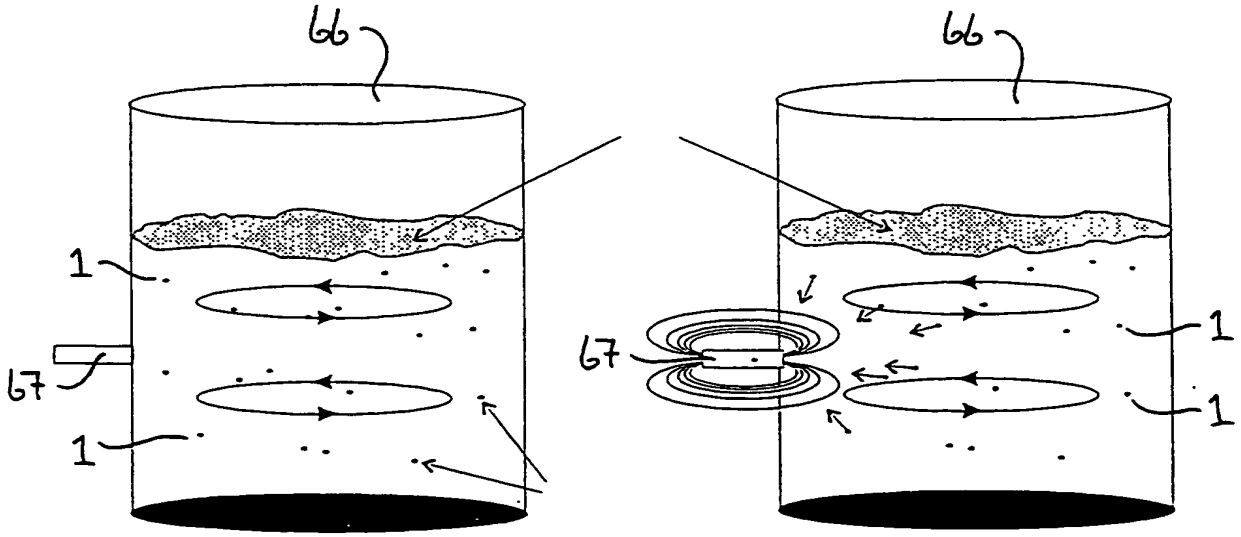


Fig. 18

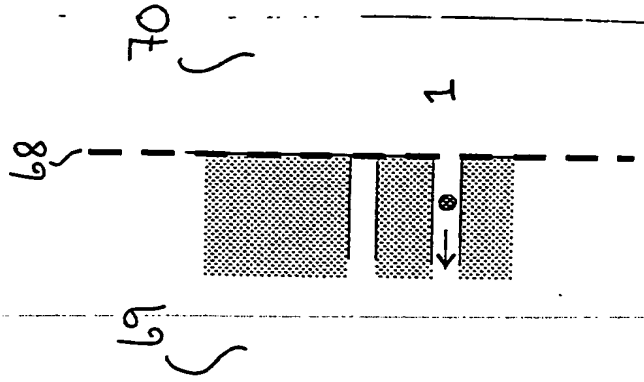


Fig. 19c

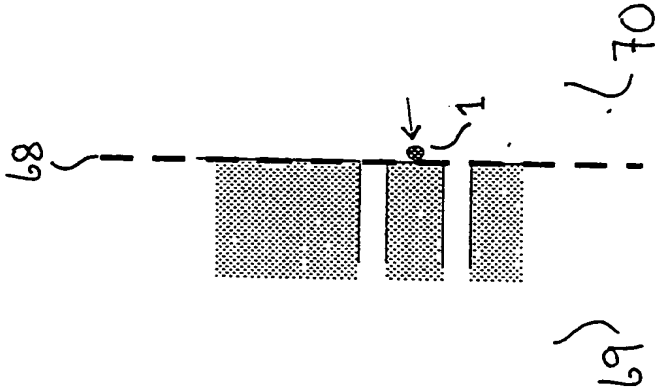


Fig. 19b

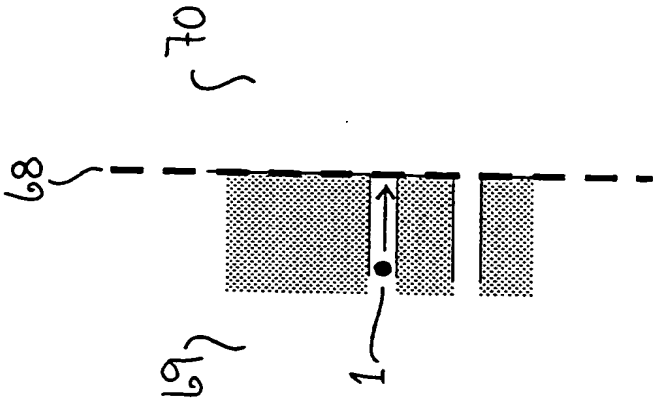


Fig. 19a

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G01N 35/00

A1

(11) International Publicati n Number: WO 99/49319

(43) International Publicati n Date: 30 September 1999 (30.09.99)

(21) International Application Number: PCT/IB99/00522

(22) International Filing Date: 25 March 1999 (25.03.99)

(30) Priority Data:
0424/98 25 March 1998 (25.03.98) DK

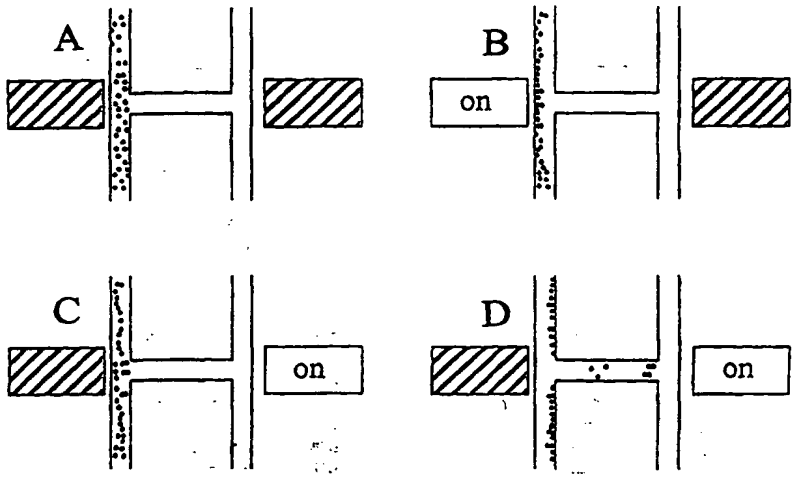
(71)(72) Applicants and Inventors: ØSTERGAARD, Steen [DK/DK]; Skovlyporten 10, st. 4, DK–2840 Holte (DK). BLANKENSTEIN, Gert [DE/DE]; Neuer Graben 11, D–44139 Dortmund (DE).

(74) Agent: OSTENFELD PATENTBUREAU A/S; Bredgade 41, P.O. Box 1183, DK–1011 Copenhagen K (DK).

(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MICRO SYSTEM AND METHOD FOR FIELD MANIPULATION OF PARTICLES



(57) Abstract

The present invention pertains to a micro system comprising a system of operably linked, interconnected compartments wherein at least one reagent immobilised on at least one particle is capable of contacting an analyte comprised in a liquid carrier. The micro system comprises i) at least one particle with surface properties suitable for immobilising at least one reagent thereon, ii) at least one reagent suitable for being immobilised on the surface of the at least one particle, iii) a first compartment for storage of the at least one particle, iv) a second compartment in which the liquid sample may interact with the reagent immobilised on at least one particle, each of said first and second compartments having at least one opening for passing liquids between the compartment and the exterior, and v) means for subjecting at least part of the system to a field so as to move at least one particle between said first and said second compartment, and vi) a passage defined between said first compartment and said second compartment so as to allow at least one particle to be moved from one of said compartments to the other through said passage. There is also provided a method related.

INTERNATIONAL SEARCH REPORT

Inte· onal Application No ·
PCT/IB 99/00522

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 - G01N35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N B01L B03C C12Q B01J C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 10267 A (BLANKENSTEIN GERT ;TECHNICAL UNIVERSITY OF DENMAR (DK)) 12 March 1998	1-5,7,9, 10,12, 14,15, 17-19, 61-67
A	see page 5, line 8 - page 5, line 34	24,35
A	see page 6, line 8 - page 6, line 12	51-53
A	see page 7, line 25 - page 9, line 20 see page 10, line 25 - page 10, line 29 see page 11, line 23 - page 11, line 28	39-41,45
A	see page 12, line 4 - page 12, line 7	54
A	see page 14, line 16 - page 14, line 27	60
A	see page 18, line 29 - page 20, line 22	31,32, 37,38, 43,44
A	see page 21, line 8 - page 21, line 16	40
A	see page 21, line 36 - page 23, line 28	46,47
A	see page 23, line 34 - page 23, line 37	25-27,36
A	see page 25, line 36 - page 26, line 27 -/--	28-30,

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1999	25/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Koch, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IB 99/00522

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	see page 28, line 5 - page 28, line 17 see page 33, line 23 - page 34, line 19	45,58,60 48,49,59
A	see page 34, line 29 - page 35, line 9 see figures 2,3,5-7,9 see figures 11,12,14,15	55-57
X	WO 93 24231 A (BIOSITE DIAGNOSTICS INC) 9 December 1993 & US 5 885 527 A (BUECHLER K. F.) 23 March 1999 see column 1, line 23 - column 1, line 28 see column 4, line 43 - column 4, line 57 see column 5, line 1 - column 7, line 14 see column 7, line 53 - column 8, line 16 see column 8, line 59 - column 8, line 65 see column 10, line 40 - column 11, line 2 see column 12, line 32 - column 13, line 6 see column 21, line 63 - column 22, line 36 see figures 1-4	1-3,9, 10,12, 16,17,20
X	WO 93 22053 A (UNIV PENNSYLVANIA) 11 November 1993 see page 5, line 8 - page 6, line 2 see page 7, line 21 - page 9, line 25 see page 18, paragraph 1 see page 20, line 4 - page 20, line 32 see page 22, paragraph 2 - page 24, paragraph 1 see page 25, paragraph 2 - page 26, paragraph 1 see figures 1-18	61-65
P,A	WO 98 46438 A (BOUSSE LUC ;CHOW CALVIN Y H (US); KNAPP MICHAEL R (US); PARCE J WA) 22 October 1998 & US 5 885 470 A (BOUSSE LUC ET AL) 23 March 1999 see column 1, line 28 - column 2, line 43 see column 3, line 5 - column 3, line 25 see column 3, line 61 - column 4, line 34 see column 6, line 52 - column 7, line 34 see column 10, line 26 - column 12, line 44 see column 13, line 44 - column 14, line 29 see figures 1,2	1-3,5,6, 12,17, 19,20, 24-26, 34,35, 37,40, 45,51, 52,59,60

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/00522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9810267 A	12-03-1998	AU 4113297 A	26-03-1998
		NO 991051 A	27-04-1999
WO 9324231 A	09-12-1993	US 5458852 A	17-10-1995
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		JP 7506430 T	13-07-1995
		JP 7506431 T	13-07-1995
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		WO 9322421 A	11-11-1993
		WO 9322055 A	11-11-1993
		WO 9322058 A	11-11-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/00522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9322053 A		US 5635358 A	03-06-1997
WO 9846438 A	22-10-1998	US 5885470 A	23-03-1999
		AU 7248498 A	11-11-1998

Copy for the Elected Office (EO/US)

PCT/IB99/005:

PATENT COOPERATION TREATY

BEST AVAILABLE COPY

PCT

From the INTERNATIONAL BUREAU

To:

HØIBERG APS
Nørre Farimagsgade 37
DK-1364 Copenhagen K
DANEMARK

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 24 November 1999 (24.11.99)	
Applicant's or agent's file reference 29511 JL/HK	**IMPORTANT NOTIFICATION**
International application No. PCT/IB99/00522	**International filing date** (day/month/year) 25 March 1999 (25.03.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

OSTENFELD PATENTBUREAU A/S
Bredgade 41
P.O. Box 1183
DK-1011 Copenhagen K
Denmark

State of Nationality:

State of Residence:

Telephone No.: +45 33 15 61 18

Facsimile No.: +45 33 15 41 65

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

HØIBERG APS
Nørre Farimagsgade 37
DK-1364 Copenhagen K
Denmark

State of Nationality:

State of Residence:

Telephone No.: +45 3332 0337

Facsimile No.: +45 3332 0384

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Philippe Bécamel Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

002971053

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To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year) 18 November 1999 (18.11.99)	
International application No. PCT/IB99/00522	**Applicant's or agent's file reference** 29511 JL/HK
International filing date (day/month/year) 25 March 1999 (25.03.99)	**Priority date** (day/month/year) 25 March 1998 (25.03.98)
Applicant ØSTERGAARD, Steen et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   21 October 1999 (21.10.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

H. Zhou

Telephone No.: (41-22) 338.83.38

8.16.

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
29511 JL/HK		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 99/00522	25/03/1999	25/03/1998
Applicant		
ØSTERGAARD, Steen et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 6

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [X] because this figure better characterizes the invention.

   [ ] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The abstract changed as follows :
Line 15 : after "provided a method" insert "related" and after "method" delete until line 18 "sample."

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
[redacted]/IB 99/00522

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N B01L B03C C12Q B01J C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 10267 A (BLANKENSTEIN GERT ;TECHNICAL UNIVERSITY OF DENMAR (DK)) 12 March 1998	1-5,7,9, 10,12, 14,15, 17-19, 61-67
A	see page 5, line 8 - page 5, line 34	24,35
A	see page 6, line 8 - page 6, line 12	51-53
A	see page 7, line 25 - page 9, line 20 see page 10, line 25 - page 10, line 29 see page 11, line 23 - page 11, line 28	39-41,45
A	see page 12, line 4 - page 12, line 7	54
A	see page 14, line 16 - page 14, line 27	60
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1999	25/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Koch, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	see page 28, line 5 - page 28, line 17 see page 33, line 23 - page 34, line 19	48,49,59
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File RS 101854

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G01N
B01L
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The present search report has been drawn up for all claims

Date of completion of the search	Examiner
18 January 1999	Koch, A

CATEGORY OF CITED DOCUMENTS

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Date of mailing *(day/month/year)*	27.06.2000
Applicant's or agent's file reference P 414 PC00	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/00522	25/03/1999	25/03/1998

Applicant
STERGAARD, Steen et al.

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2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

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